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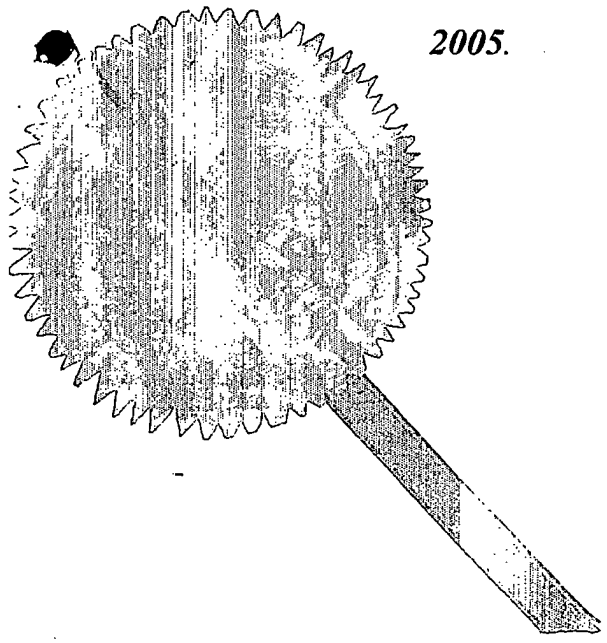
GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI
BOUDHIK SAMPADA BHAWAN,
PLOT NO. 32, SECTOR – 14,
NEW DELHI - 110 075.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Provisional Specification*** *filed in connection with Patent Application No.**211/Del/2005** dated **02nd February 2005**.*



Witness my hand this 05th day of July 2006.

(P.K. PATNI)
Deputy Controller of Patents & Designs

0211-DEL-05

02 FEB 2005

FORM 1 THE PATENT ACT 1970 (39 of 1970) & The Patents Rules, 2003 APPLICATION FOR GRANT OF PATENT (See section 7, 54 and 135 and Rule 20(1)	(FOR OFFICE USE ONLY) Application No._____ Filing Date:_____ Amount of Fee Paid: Rs._____ CBR No. _____ Signature: _____

1. APPLICANT (S)
RANBAXY LABORATORIES LIMITED, an Indian Company, incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi – 110019, India.

2. INVENTOR (S)
VENKATA P. PALLE, ASHWANI KUMAR VERMA, RAKESH KUMAR SINGH, SANJAY MALHOTRA, YOGESH BHASKARRAO WAMAN, ARTI WALIA, ABHIJIT RAY, GEETA SHARMA
All Indian Nationals, of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon 122001 (Haryana), India.

3. TITLE OF THE INVENTION
"ANTI-INFLAMMATORY AGENTS"

4. ADDRESS FOR CORRESPONDENCE OF APPLICANT/ AUTHORIZED AGENT IN INDIA:
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Gurgaon–122001, Haryana, India.
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Fax Nos. (0124) 2342027, 5016855

5. PRIORITY PARTICULARS OF THE APPLICATION(S) FILED IN CONVENTION COUNTRY: NOT APPLICABLE

6. PARTICULARS FOR FILING PATENT COOPERATION TREATY (PCT) NATIONAL PHASE APPLICATION: NOT APPLICABLE

7. PARTICULARS FOR FILING DIVISIONAL APPLICATION: NOT APPLICABLE

8. PARTICULARS FOR FILING PATENT OF ADDITION: NOT APPLICABLE

9. DECLARATIONS:

(i) **Declaration by the Inventor(s):**

We, the above named inventor(s) is/are the true and first inventor(s) for this invention and declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi – 110019, India, is our assignee or legal representative.

Date	Signature(s)	Name (s)
07-01-05		Venkata P. Palle
07.01.05		Ashwani Kumar Verma
07-01-05		Rakesh Kumar Singh
07-01-2005		Sanjay Malhotra
07.01.05		Yogesh Bhaskarrao Waman
07-01-05		Arti Walia
7 Jan 05		Abhijit Ray
07-01-05		Geeta Sharma

(ii) **Declaration by the applicant(s) in the convention country:**

We, the applicant, in the convention country declare that the applicant herein is our assignee or legal representative.

Date : _____

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

(iii) **Declaration by the Applicant(s) :**

We, the applicant (s) hereby declare (s) that :-

- We are in possession of the above-mentioned invention.
- The provisional / complete specification relating to the invention is filed with this application.
- The invention as disclosed in the specification uses the biological material from India and necessary permission from the competent authority shall be submitted by us before the grant of the patent to us.
- There is no lawful ground of objection to the grant of the Patent to us.
- We are the assignee or legal representative of true and first inventors.
- The application or each of the applications, particulars of which are given in Para-5 was the first application in convention country / countries in respect of our invention.
- We claim the priority from the above mentioned application(s) filed in convention country/ countries and state that no application for protection in respect of the invention had been made in a convention country before that date by us or by any person from which we derive the title.
- Our application in India is based on International application under Patent Cooperation Treaty (PCT) as mentioned in Para-6.

◊ The application is divided out of our application particulars of which are given in Para-7 and pray that this application may be treated as deemed to have been filed on _____ under sec.16 of the Act.

◊ The said invention is an improvement in or modification of the invention particulars of which are given in Para-8.

10. **FOLLOWING ARE THE ATTACHMENTS WITH THE APPLICATION:**

(a) Provisional specification / Complete specification
(b) Complete specification (in conformation with the international applications)/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies), No. of Pages _____ No. of claims _____.
(c) Drawings (in conformation with the international application)/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies), No. of sheets _____.
(d) Priority documents
(e) Translation of priority documents / Specification/International Search Report
(f) Statement and undertaking on Form 3
(g) Power of Authority
(h) Declaration of inventorship on Form 5
(i) Sequence listing in electronic form
(j) _____

Fee Rs. _____in Cash/Cheque/Bank Draft bearing No. _____

Date _____, on HDFC Bank Limited, Gurgaon.

We hereby declare that to the best of our knowledge, information and belief the fact and matters stated herein are correct and we request that a patent may be granted to us for the said invention.

Dated this 31ST day of **January, 2005.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

To

The Controller of Patent
The Patent Office
New Delhi

FORM 2

The Patents Act, 1970

(39 of 1970)

&

The Patent Rules, 2003

PROVISIONAL SPECIFICATION

(See Section 10 and Rule 13)

ANTI-INFLAMMATORY AGENTS

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

FIELD OF THE INVENTION

The present invention relates to novel azabicyclo derivatives as anti-inflammatory agents.

The compounds of this invention can be useful for inhibition and prevention of inflammation and associated pathologies including inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-I diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

This invention also relates to pharmacological compositions containing the compounds of the present invention and the methods of treating sepsis, rheumatoid arthritis, inflammatory bowel disease, type-I diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis, and other inflammatory and/or autoimmune disorders, using the compounds.

BACKGROUND OF THE INVENTION

During the last decade, numerous studies have focused on the roles played by cytokines, a unique class of intercellular regulatory proteins, in the pathogenesis of many diseases. Cytokines play a crucial role in initiating, maintaining, and regulating immunological and inflammatory processes. Advances in our understanding of their role in immune and inflammatory disorders have led to the development of cytokine-based therapies-that is, therapies that aim to inhibit or restore the activity of specific cytokines. Today, drugs that block inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), are among the most successful agents being introduced to the market.

Elevated levels of proinflammatory cytokines viz TNF-α and IL-β are associated with the pathogenesis of many immune mediated inflammatory disorders like sepsis, rheumatoid arthritis, inflammatory bowel disease, type-I diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis. Inflammation is regulated by a large number of pro- and anti-inflammatory mediators, which include cytokines, eicosanoids, nitric oxide, and reactive oxygen species. The central role of these

inflammatory mediators in the pathogenesis of both chronic and acute inflammatory diseases is well documented. Until a few years ago, inflammatory disorders were treated primarily with relatively non-selective anti-inflammatory agents, such as corticosteroids and various non-steroidal anti-inflammatory drugs. In recent years, novel therapies have been developed that specifically interfere with the action of selected pro-inflammatory mediators, such as TNF-α and PGE-2. These specific anti-inflammatory therapies have already proven to be very successful in the treatment of rheumatoid arthritis, inflammatory bowel disease, and several other inflammatory diseases.

The development of protein-based therapies that inhibit the activities of tumour-necrosis factor-α (TNF-α), including etanercept (Enbrel; Amgen/Wyeth), infliximab (Remicade; Centocor), and adalimumab (Humira; Abbott), has been an important advancement in the treatment of autoimmune diseases such as rheumatoid arthritis. The approval of Kineret - an interleukin-1 (IL-1) receptor antagonist - further indicates the clinical activity of protein-based therapies that regulate cytokine activities. However, current injectable therapies have associated limitations and risks, including the potential for increased malignancies and infections and increased congestive heart failure. Studies in rodent models have provided evidence that targeting specific pathways involved in TNF-α activities are effective approaches to interrupting the pro-inflammatory process. Oral small molecules that regulate these pathways should be the next significant advancement in the treatment of chronic inflammatory diseases when used either as a monotherapy or in combination with the current injectables.

Numerous studies have now clearly established that the pathogenesis of inflammatory diseases requires cytokine-mediated communication between endothelial cells, infiltrating leukocytes, resident macrophages, mast cells, epithelial cells and osteoclasts. The p38 mitogen activated protein kinase (p38MAPK) regulates cytokine levels and therefore plays a central role in both the cellular infiltration and activation responses associated with inflammatory diseases.

The p38 MAPK is a member of a large family of MAPK's whose signalling pathways also include the extracellular regulated kinases (ERK) & the c-jun N terminal kinases (JNK). MAP kinases are Serine Threonine Kinases that transduce environmental stimuli to the nucleus and they themselves are activated by upstream MAPK kinases by phosphorylation on both Tyrosine and Threonine residues. The MAPK pathways are involved in alterations in cell physiology resulting from a variety of stimuli and control cell death, cell cycle machinery, gene transcription and protein translation. p38α MAPK was first identified as a tyrosine phosphorylated protein in LPS (Lipopolysaccharide) stimulated macrophages. The human p38α MAPK was identified as the target of pyridinyl imidazole compounds (cytokine suppressive anti-inflammatory drugs) that were known to block TNF-α and IL-1 release from LPS stimulated monocytes. After the cloning of first p38 MAPK (p38α), additional members of the p38 MAPK family were cloned by homology, including the p38α, p38β and p38γ.

The p38 pathway controls the activity of multiple transcription factors and the expression of many genes. There is ample evidence implicating a pivotal role for p38 in inflammatory processes mediated by IL-1 and TNF-α. p38 inhibitors have been shown to effectively block both TNF-α and IL-1 biosynthesis by LPS stimulated human monocytes.

In addition, p38 MAPK also plays a role in the production of IL-4, IL-6, IL-8 and IL-12. p38 MAPK is also critical for cell response to certain cytokines. Treatment of human neutrophils with GM-CSF, TNF-α or TGF-α results in p38 activation. GM-CSF and TNF-α are potent enhancers of neutrophil respiratory activity suggesting a role for p38 MAPK in respiratory burst.

p38 has also been implicated in the induction of cyclooxygenase-2 (COX-2) in LPS induced monocytes. COX-2 enzyme is the key enzyme in the production of prostaglandins from arachidonic acid. Inhibitors of p38 MAP kinase are also expected to inhibit COX-2 expression. Accordingly inhibitors of cytokine synthesis would be expected to be effective in disorders currently treated with NSAID's. These disorders

include acute and chronic pain as well as symptoms of inflammation and cardiovascular disease.

Compounds, which modulate release of one or more of the aforementioned inflammatory cytokines, can be useful in treating diseases associated with the release of these cytokines.

PCT Application WO01/44258 discloses bone-targeting groups useful for treating a variety of disorders and conditions. PCT Application WO02/18380 and U.S. patent Nos. US 6,518276 and US 6,506,749 discloses 7-oxopyridopyrimidines as inhibitors of cell proliferation. PCT Application WO03/057165 describes the compositions and methods for prevention and treatment of amyloid-β-peptide related disorders. US 6,316,464 disclose compounds as p-38 kinase inhibitors. US 6,451,804 discloses heteroalkylamino substituted bicyclic nitrogen heterocycles. US 6,696,566 discloses 6-substituted pyrido-pyrimidines useful for the treatment of p-38 mediated disorders. US 6,479,507 disclose p-38 kinase inhibitors. U.S. Application 2003/0153586 discloses 7-oxo-pyridopyridopyrimidines for the treatment of p-38 mediated disorders. WO 2003/00270 discloses pyridopyrimidones and uses thereof. US 6,630,485 discloses p-38 kinase inhibitors, pharmaceutical compositions containing them, method for their use, and methods for preparing these compounds. WO 20040019210 discloses pyridopyrimidine, naphthyridines and pyriodopyrazine derivatives as cyclin dependent kinase and tyrosine kinase inhibitors.

SUMMARY OF THE INVENTION

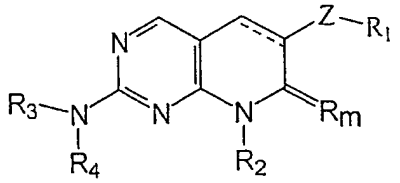
The present invention provides novel azabicyclo derivatives, which can be used for the inhibition and prevention of inflammation and associated pathologies such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-I diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

Pharmaceutically acceptable salts, pharmaceutically acceptable solvates, enantiomers, diastereomers or N-oxides of these compounds having the same type of activity are also provided.

Pharmaceutical compositions containing the compounds, and which may also contain pharmaceutically acceptable carriers or diluents, which may be used for the treatment of inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

Other aspects will be set forth in accompanying description which follows and in part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect, there is provided a compound having the structure of Formula I



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers·diastereomers, N-oxides, polymorphs, metabolites;

wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl, or heterocyclylalkyl;

when R_m is oxygen or sulphur

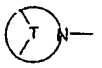
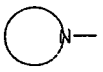
R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl;

when R_m is -NH, -N-acyl, -N(CN), -$N(NO_2)$, -$C(R_3)_2$ or -$CH(NO_2)$

R_2 is hydroxy, alkoxy, aryloxy, -CHO, -CN, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, halogen, aryl, aralkyl, acyl, heteroaryl, heterocyclyl, -SO_2R_5, -$COOR_6$, -$C(=O)NR_xR_y$, -NR_xR_y or -$OC(=O)NR_xR_y$ or -$NHC(=O)R_x$;

---- represents a single bond or a double bond;

R_3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heteroarylalkyl or heterocyclylalkyl;

R_4 is  (wherein  represents a cyclic ring containing 4-8 carbon atoms wherein 1-3 carbon atoms may optionally be replaced by heteroatoms selected from oxygen, -NH or sulphur; T is -$(CH_2)_n$-, -$CH(Q)CH_2$-, -$CH_2CH(Q)CH_2$-, -$CH(Q)$-, -CH_2-O-CH_2-, -CH_2-NH-CH_2-, -CH_2-$N(CH_3)$-CH_2);

n is an integer selected from 0-3 (wherein when n is zero then T represents a direct bond);

R_5 is alkyl, alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p and R_q are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl; R_p and R_q may also together join to form a heterocyclyl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl;

R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroarylalkyl or heterocyclylalkyl;

Z is a direct bond, oxygen, sulphur, -NH or -$(CH_2)_n$;

R_x and R_y are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, $-SO_2R_5$ (wherein R_5 is the same as defined above), heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl;

Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl.

In accordance with second aspect, there is provided a method for the treatment of mammal suffering from inflammation and associated pathologies.

In accordance with third aspect, there is provided a method for the treatment of mammal suffering from inflammatory diseases and associated pathologies including sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

In accordance with fourth aspect, there are provided a pharmaceutical compositions containing the compounds, and which may also contain pharmaceutically acceptable carriers or diluents, which may be used for the treatment of inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.

In accordance with fifth aspect, there is provided a process for the preparation of compounds disclosed herein.

In accordance with sixth aspect, the compounds of the present invention are screened as p38 kinase inhibitors.

The following definitions apply to terms as used herein:

The term "alkyl" unless and otherwise specified refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-hexyl, n-decyl, tetradecyl, and the like.

It may further be substituted with one or more substituents selected from the group consisting of alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, thiocarbonyl, substituted thiocarbonyl, carboxy, $-COOR_6$ (wherein R_6 is the same as defined earlier), thiol, aryloxy, alkoxyamino, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, (wherein R_x and R_y are the same as defined earlier), nitro, $-S(O)_nR_5$ (wherein R_5 is alkyl, aryl or heteroaryl and n is 0, 1 or 2). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, carboxy, $-COOR_6$ (wherein R_6 is the same as defined earlier), $-NR_xR_y$, $-C(=O)NR_xR_y$, $-O-C(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, $-NHC(=O)OR_6$, (wherein R_x and R_y are the same as defined earlier), hydroxy, alkoxy, halogen, $-CF_3$, cyano, and $-S(O)_nR_5$ (where n and R_5 are the same as defined earlier).

Alkyl group as defined above may also be interrupted by 1-5 atoms of groups independently chosen from oxygen, sulfur and $-NR_a$ (where R_a is chosen from hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl).

The term "alkenyl" unless and otherwise specified refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 20 carbon atoms with cis or trans geometry. Preferred alkenyl groups include ethenyl or vinyl, 1-propylene or allyl, iso-propylene, bicyclo[2.2.1]heptene, and the like. In the event that alkenyl is attached to the heteroatom, the double bond cannot be alpha to the heteroatom.

It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, $-CF_3$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, thiocarbonyl, substituted thiocarbonyl, carboxy, $-COOR_6$ (wherein R_6 is the same as defined earlier), thiol, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl,

alkoxyamino, nitro, $S(O)_nR_5$ (wherein n and R_5 are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, $-COOR_6$ (wherein R_6 is the same as defined earlier), hydroxy, alkoxy, halogen, $-CF_3$, cyano, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier) and $-S(O)_nR_5$ (where R_5 and n are the same as defined earlier).

The term "alkynyl" unless and otherwise specified refers to a monoradical of an unsaturated hydrocarbon, preferably having from 2 to 20 carbon atoms. Preferred alkynyl groups include ethynyl, propargyl or propynyl, and the like. In the event that alkynyl is attached to the heteroatom, the triple bond cannot be alpha to the heteroatom. It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkoxy, cycloalkyl, acyl, acylamino, alkoxyamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, thiocarbonyl, substituted thiocarbonyl, $-CF_3$, carboxy, $-COOR_6$ (wherein R_6 is the same as defined earlier), thiol, aryl, aralkyl, aryloxy, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), $-S(O)_nR_5$ (wherein n and R_5 are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, $-COOR_6$ (wherein R_6 is the same as defined earlier), hydroxy, alkoxy, halogen, $-CF_3$, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-O-C(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), cyano and $-S(O)_nR_5$ (wherein R_5 and n are the same as defined earlier).

The term "cycloalkyl" refers to cyclic alkyl groups containing 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless or otherwise constrained by the definition. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring structures such as adamantanyl, and bicyclo [2.2.1] heptane, or cyclid alkyl groups to

which is fused with an aryl group, for example indane or tetrahydro-naphthalene and the like.

It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, alkoxyamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, thiocarbonyl, substituted thiocarbonyl, carboxy, $-COOR_6$ (wherein R_6 is the same as defined earlier), thiol, aryl, aralkyl, aryloxy, $-NR_xR_y$, $-NHC(=O)NR_xR_y$, $-C(=O)NR_xR_y$, $-O-C(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $-CF_3$, $-S(O)_nR_5$ (wherein R_5 and n are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may optionally be further substituted by 1-3 substituents chosen from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), cyano and $-S(O)_nR_5$ (where R_5 and n are the same as defined earlier).

The term "alkoxy" denotes the group O-alkyl wherein alkyl is the same as defined above.

The term "aralkyl" refers to aryl linked through alkyl (wherein alkyl is the same as defined above) portion and the said alkyl portion contains carbon atoms from 1-6 and aryl is as defined below.

The term "aryl" herein refers to a carbocyclic aromatic group, (for example, phenyl, biphenyl or naphthyl ring and the like optionally substituted with 1 to 3 substituents selected from the group consisting of halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, acylamino, alkoxyamino, thiocarbonyl, substituted thiocarbonyl, alkynyl, alkoxycarbonylamino, cycloalkyl, alkoxy, acyl, aryloxy, cyano, $-CF_3$, nitro, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier), carboxy, $-S(O)_nR_5$ (where R_5 and n are the same as defined earlier), $-COOR_6$ (wherein R_6 is the same as defined earlier), heterocyclyl, heteroaryl, heterocyclylalkyl or heteroarylalkyl.

The term "carboxy" as defined herein refers to –C(=O)OH.

The term "aryloxy" denotes the group O-aryl, wherein aryl is as defined above.

The term "heteroaryl" unless and otherwise specified refers to monocyclic aromatic ring structure containing 5 or 6 carbon atoms, a bicyclic or a tricyclic aromatic group having 8 to 10 carbon atoms, with one or more heteroatom(s) independently selected from the group consisting of N, O and S optionally substituted with 1 to 3 substituent(s) selected from the group consisting of halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, acylamino, thiocarbonyl, substituted thiocarbonyl, alkoxyamino, alkoxycarbonylamino, cycloalkyl, acyl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, carboxy, $-S(O)_nR_5$ (where R_5 and n are the same as defined earlier), $-CF_3$, $-COOR_6$ (wherein R_6 is the same as defined earlier), aryl, alkoxy, aralkyl, cyano, nitro, $-NR_xR_y$, $-C(=O)NR_xR_y$, $-NHC(=O)NR_xR_y$ and $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier). Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, xanthene, benzoxazolyl, and the like.

The term "heterocyclyl" unless and otherwise specified refers to a non aromatic monocyclic, bicyclic (fused, bridged, or spiro) or tricyclic cycloalkyl group having 5 to 10 atoms in which 1 to 3 carbon atoms in a ring are replaced by heteroatoms selected from the group comprising of O, S and N, and are optionally benzofused or fused heteroaryl of 5-6 ring members and the said heterocyclyl group is optionally substituted wherein the substituents are selected from the group consisting of halogen (F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, thiocarbonyl, substituted thiocarbonyl, aryl, alkoxy, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl, cyano, alkoxyamino, acylamino, alkoxycarbonylamino, nitro, $-CF_3$, carboxy, $-S(O)_nR_5$ (where R_5 and n are the same as defined earlier), $-COOR_6$ (wherein R_6 is the same as defined earlier), $-NHC(=O)NR_xR_y$, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$ (wherein R_x and R_y are the same as defined earlier). Examples of heterocyclyl groups are tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, isoxazolinyl, piperidinyl, morpholine, piperazinyl, dihydrobenzofuryl, azabicyclohexyl, azabicyclooctyl, dihydroindolyl, and the like.

"Heteroarylalkyl" refers to heteroaryl (wherein heteroaryl is same as defined earlier) linked through alkyl (wherein alkyl is the same as defined above) portion and the said alkyl portion contains carbon atoms from 1-6.

"Heterocyclylalkyl" refers to heterocyclyl (wherein heterocyclyl is same as defined earlier) linked through alkyl (wherein alkyl is the same as defined above) portion and the said alkyl portion contains carbon atoms from 1-6.

"Acyl" refers to –C(=O)R'' wherein R'' is selected from the group hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

"Thiocarbonyl" refers to –C(=S)H.

"Substituted thiocarbonyl" refers to -C(=S)R'', wherein R'' is selected from alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl, amine or substituted amine.

The term "leaving group" generally refers to groups that exhibit the desirable properties of being labile under the defined synthetic conditions and also, of being easily separated from synthetic products under defined conditions. Examples of such leaving groups includes but not limited to halogen (F, Cl, Br, I), triflates, tosylate, mesylates, alkoxy, thioalkoxy, hydroxy radicals and the like.

The term "Protecting Groups" is used herein to refer to known moieties, which have the desirable property of preventing specific chemical reaction at a site on the molecule undergoing chemical modification intended to be left unaffected by the particular chemical modification. Also the term protecting group, unless or other specified may be used with groups such as hydroxy, amino, carboxy and example of such groups are found in T.W. Greene and P.G.M. Wuts: "Protective Groups in Organic Synthesis", 2nd Edn. John Wiley and Sons, New York, N.Y., which is incorporated herein by reference. The

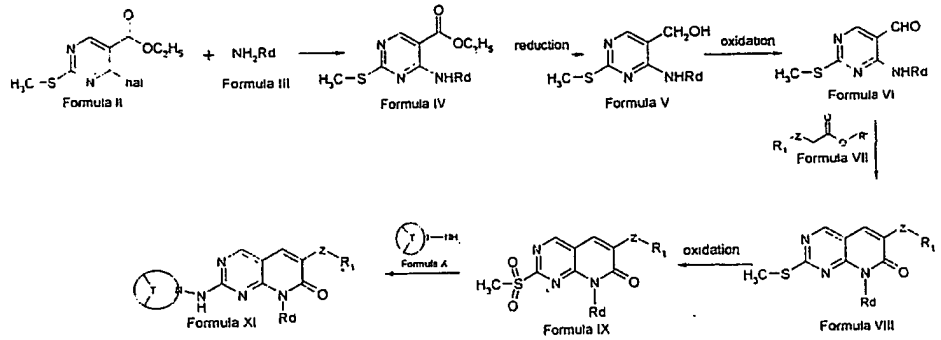
species of the carboxylic protecting groups, amino protecting groups or hydroxy protecting group employed is not so critical so long as the derivatised moiety/moieties is/are stable to conditions of subsequent reactions and can be removed at the appropriate point without disrupting the remainder of the molecule.

The term "pharmaceutically acceptable salts" refers to derivatives of compounds that can be modified by forming their corresponding acid or base salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acids salts of basic residues (such as amines), or alkali or organic salts of acidic residues (such as carboxylic acids), and the like.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention may be prepared by techniques well known in the art and familiar to a practitioner skilled in art of this invention. In addition, the compounds of the present invention may be prepared by the process described herein, this process is not the only means by which the compounds described may be synthesised. Further, the various synthetic steps described herein may be performed in an alternate sequence in order to give the desired compounds.

Scheme I



The compounds of Formulae XI and XII, may be prepared by following the reaction sequence as depicted in Scheme I, thus a compound of Formula II [wherein hal is halogen (Cl, Br or I)] is reacted with a compound of Formula III (wherein R_d is optionally substituted alkyl, cycloalkyl, aralkyl or aryl) to give a compound of Formula IV, which

undergoes reduction to give a compound of Formula V, which is further oxidized to give a compound of Formula VI, which is reacted with an ester of Formula VII (wherein R' is alkyl; R_1 and Z are the same as defined earlier) to give a compound of Formula VIII, which is oxidized to give a compound of Formula IX, which is reacted with a compound of Formula X [wherein T is the same as defined earlier], to give a compound of Formula XI.

The reaction of a compound of Formula II with a compound of Formula III to give a compound of Formula IV is carried out in an organic solvent, for example tetrahydrofuran, dimethylformamide, dioxane or diethyl ether in the presence of a base for example, triethylamine, N-ethyldiisopropylamine, N-methylmorpholine or pyridine.

The compound of Formula IV is reduced to give a compound of Formula V in an organic solvent for example, tetrahydrofuran, dimethylformamide, dioxane or diethylether with reducing agent for example, lithium aluminium hydride, lithium borohydride, sodium cyanoborohydride or sodium borohydride.

The oxidation of a compound of Formula V to give a compound of Formula VI can be carried out in an organic solvent for example, dichloromethane, dichloroethane, carbon tetrachloride or chloroform with an oxidizing agent for example, manganese dioxide, potassium permanganate, Dess Martin periodinane (DMP), pyridinium dichromate (PDC), pyridinium chlorochromate (PCC) or chromic anhydride, although numerous other methods can be employed (see, for example, Advanced Organic Chemistry, 4th Edn., Merck, John Wiley & Sons, 1992).

The reaction of a compound of Formula VI with a compound of Formula VII to give a compound of Formula VIII can be carried out in an organic solvent for example, N-methylpyrrolidinone, dimethylformamide, tetrahydrofuran, diethylether or dioxane in the presence of a base for example, potassium carbonate, sodium carbonate or lithium carbonate, potassium bicarbonate, lithium bicarbonate or sodium bicarbonate.

The oxidation of a compound of Formula VIII to give a compound of Formula IX can be carried out with m-chloroperbenzoic acid or oxone ($KHSO_5$) in an organic solvent for example, chloroform, carbon tetrachloride, dichloromethane, ethanol or tetrahydrofuran.

The reaction of a compound of Formula IX with a compound of Formula X to give a compound of Formula XI can be carried in the presence of a base for example, pyridine, N-methylmorpholine, N-ethyldiisopropylamine, sodium hydride or triethylamine.

Alternatively, in some cases rather than using a compound of Formula IX, a compound of Formula VIII can be reacted directly with a compound of Formula X to give a compound of Formula XI.

Particular compounds are mentioned below:

6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 1),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 2),

6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 3),

6-(2,4-Difluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 4),

6-(3-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 5),

6-(4-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 6),

6-(4-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 7),

6-(4-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 8),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-benzylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 9),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 10),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-*tert*-butylbenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 11),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-trifluoromethoxybenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 12),

6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 13),

6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-chloro-2-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 14),

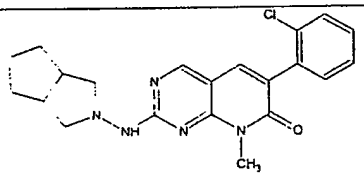
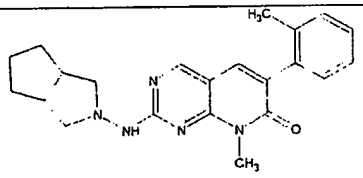
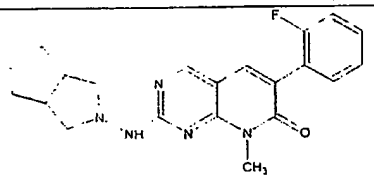
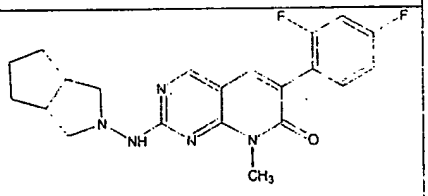
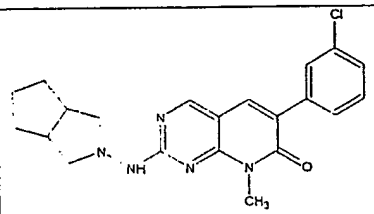
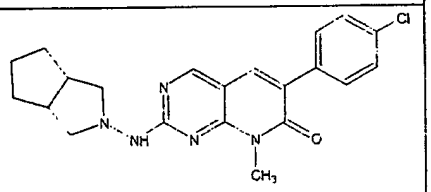
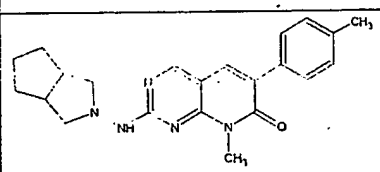
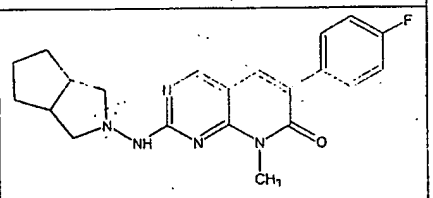
6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-benzylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 15),

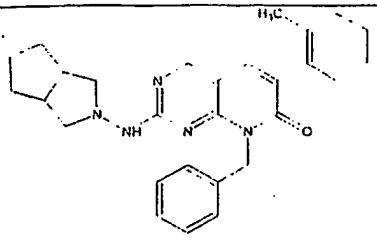
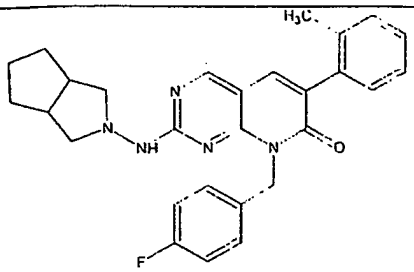
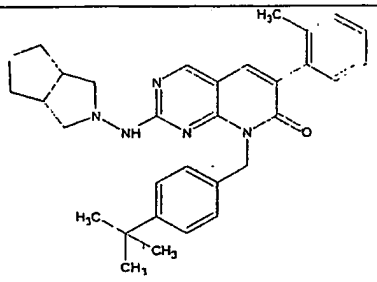
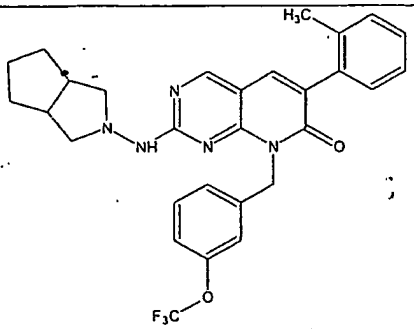
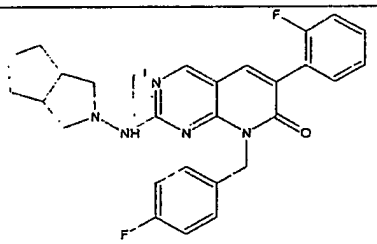
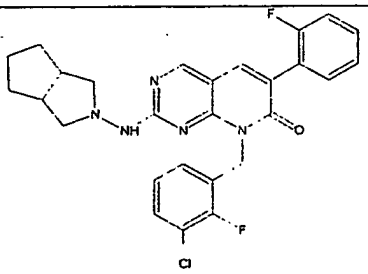
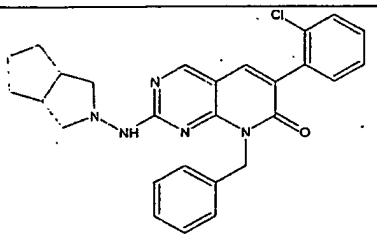
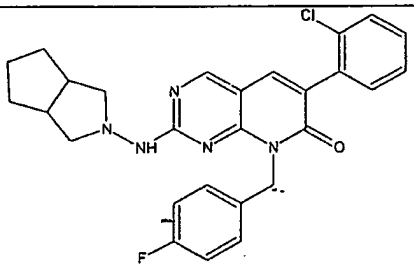
6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 16),

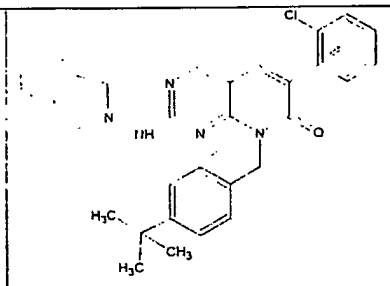
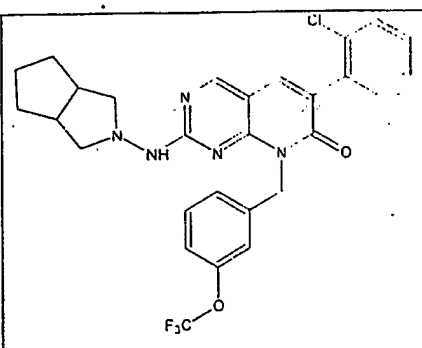
6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-*tert*-butylbenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 17).

6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-trifluoromethoxybenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 18).

Preferred compounds according to the invention being produced by scheme I, are listed in table below:

Compound No	Structure	Compound No.	Structure
1.		2.	
3.		4.	
5.		6.	
7.		8.	

9.		10.	
11.		12.	
13.		14.	
15.		16.	

17.		18.	

Example set forth demonstrates the general synthetic procedure for the preparation of representative compounds. The examples are provided to illustrate particular aspect of the disclosure and should not be constrained to limit the scope of the present invention

Experimental

Example 1: Synthesis of 6-(2-chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 1)

Step a: 4-Methylamino-2-methylthio-pyrimidine-5-carboxylic acid ethyl ester

To a suspension of ethyl-4-chloro-2-methylthio-5-pyrimidine-carboxylate (commercially available) (8.0 g, 34 mmol) in dry tetrahydrofuran (60 ml), was added triethylamine (4.3 g, 42 mmol) and aqueous methylamine (40%, 3.2 g, 36.2 mmol) at room temperature and stirred for 2 hours. The organic solvent was evaporated under reduced pressure followed by addition of cold water. A white solid thus obtained was filtered, washed with water and dried under vacuum. Yield = 6.2 g.

Step b: [4-(Methylamino)-2-(methylthio)-pyrimidin-5-yl]-methanol

To a suspension of lithium aluminium hydride (1.21 g, 32 mmol) in dry tetrahydrofuran (60 ml) at -70°C, was added a solution of the compound obtained from step *a* above (6.0 g, 26 mmol) in tetrahydrofuran (20 ml) dropwise. The reaction mixture was stirred between -70°C -60°C for 1 hour and then at room temperature till completion.

The reaction mixture was cooled to 0°C and diluted with ethylacetate, followed by addition of 30% aqueous solution of sodium hydroxide dropwise. The reaction mixture was then filtered through a celite pad and washed with ethylacetate and dichloromethane. The filtrate was evaporated under reduced pressure followed by addition of water. A white solid thus obtained was filtered and dried under vacuum. Yield = 4.0 g.

Step c: 4-Methylamino-2-methylthio-pyrimidin-5-carboxldehyde

To a suspension of compound obtained from step *b* above (3.8 g, 20.7 mmol) in dichloromethane (100 ml), was added manganese dioxide (12.7 g, 145 mmol) at room temperature and stirred for 24-36 hours. The reaction mixture was filtered over a celite pad and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using ethylacetate in hexane (1:4) solvent mixture as eluent to furnish the title compound. Yield = 3.2 g.

Step d: 6-(2-Chlorophenyl)-8-methyl-2-methylthio-8H-pyrido[2,3-d]pyrimidin-7-one

To a solution of the compound obtained from step *c* above (3.2 g, 17.7 mmol) in N-methylpyrrolidinone (20 ml), was added 2-chlorophenyl acetic acid methyl ester (4.9 g, 26.6 mmol) and potassium carbonate (7.4 g, 53.04 mmol) and heated at 110°C for 2 hours. The reaction mixture was diluted with ethylacetate and poured into water. It was then extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using ethylacetate in hexane (1:3) as eluent. Yield = 3.2 g.

Step e: 6-(2-Chlorophenyl)-2-methanesulphonyl-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one

To a solution of the compound obtained from step *d* above (1.5 g, 4.7 mmol) in chloroform (20 ml) was added m-chloroperbenzoic acid (70%) (3.5 g, 14.2 mmol) at 0°C and stirred at room temperature for 30 minutes. To it was added a saturated solution of aqueous sodium bisulphate followed by aqueous sodium bicarbonate solution at 0°C. The reaction mixture was then extracted with dichloromethane and the organic layer was washed with water, dried over anhydrous sodium sulphate, filtered and evaporated under

reduced pressure. The residue thus obtained was washed thoroughly with hexane to furnish the title compound. Yield = 1.1 g

Step f: 6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-d]pyrimide-7(8H)-one

To the compound obtained from step *e* above (0.1 g, 0.286 mmol), was added 3-amino-3-azabicyclo[3.3.0]octane (commercially available) (0.116 g, 0.715 mmol) and heated to 80°C for 2 hours. The reaction mixture was diluted with dichloromethane and the compound was purified by column chromatography using (1:1) ethyl acetate: hexane as eluent to afford a yellow residue which was then further purified by preparative TLC using (15:85) ethylacetate: dichloromethane as solvent of elution. Yield = 35 mg.

m.p.: 85-87°C.

^{1}H NMR ($CDCl_3$):δ 8.55 (s, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.48-7.44 (t, 1H, J=3Hz, Ar-H), 7.35-7.30 (m, 3H, Ar-H), 3.72 (s, 3H, -NCH_3), 3.32 (brs, 2H, -NCH_2), 2.74 (brs, 2H, -NCH_2), 2.49 (brs, 2H, -2x-CH) and 1.73-1.53 (m, 6H, 3x-CH_2).

Mass spectrum (m/z, +ve ion mode): 398 [M^++1+2] and 396 [M^++1].

The analogues of 6-(2-chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 1) described below can be prepared by using appropriate amine in place of 3-amino-3-azabicyclo[3.3.0]octane, respectively, as applicable in each case.

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 2)

m.p: 69.8-79.8°C.

^{1}H NMR ($CDCl_3$ + CD_3OD):δ 9.09 (s, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.33-7.17 (m, 4H, Ar-H), 3.74 (s, 3H, -NCH_3), 2.63-2.56 (m, 6H, 2x-NCH_2 & 2x-CH), 2.21 (s, 3H, -$ArCH_3$) and 1.73-1.70 (m, 6H, 3x-CH_2).

Mass spectrum (m/z, +ve ion mode): 376 [M^++1].

6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 3),

6-(2,4-Difluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 4),

6-(3-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 5),

6-(4-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 6),

6-(4-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 7),

6-(4-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 8),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(benzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 9),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 10),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(tert-butylbenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 11),

6-(2-Methylphenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-trifluoromethoxybenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 12),

6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 13),

6-(2-Fluorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-chloro-2-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 14),

6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(benzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 15),

6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-fluorobenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 16),

6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(4-tert-butylbenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 17),

6-(2-Chlorophenyl)-2-(3-azabicyclo[3.3.0]oct-3-yl-amino)-8-(3-trifluoromethoxybenzyl)-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (Compound No. 18).

Methodology

p38 Inhibition Assays

Inhibition of phosphorylation of EGF receptor Peptide

This assay was carried out in the presence of 10 mM MgCl2, 25 mM β- glycerophosphate, 10% glycerol and 100 mM HEPES buffer at pH 7.6. For a typical IC50 determination, a stock solution was prepared containing all of the above components and activated p38 (5nM). The stock solution was aliquoted into vials. A fixed volume of DMSO or inhibitor in DMSO (final concentration of DMSO in reaction was 5%) was introduced to each vial, mixed and incubated for 15 minutes at room temperature.

EGF receptor peptide, KRELVEPLTPSGEAPNQALLR, a phosphoryl acceptor in p38-catalysed kinase reaction (1), was added to each vial to a final concentration of 200µM. The kinase reaction was initiated with ATP (100µm) and the vials were incubated at 30-degree celcius. After 30 minutes, the reactions were quenched with equal volume of 10% trifluoroacetic acid (TFA).

The phosphorylated peptide was quantified by HPLC analysis. Separation of the phosphorylated peptide from the unphosphorylated peptide was achieved on a reverse phase column (Deltapak, 5µM, C18 100D, part no. 011795) with a binary gradient of water and acetonitrile, each containing 0.1% TFA. IC50 (concentration of inhibitor yielding 50% inhibition) was determined by plotting the % activity remaining against inhibitor concentration.

Cell based Assay for TNF-α release

Method of isolation of Human Peripheral Blood Monomuclear Cells:

Human whole blood was collected in vacutainer tubes containing EDTA as an anti coagulant. A blood sample (7 ml) was carefully layered over 5 ml PMN Cell Isolation Medium (Robbins Scientific) in a 15 ml round bottom centrifuge tubes. The sample was centrifuged at 450-500 x g for 30 - 35 minutes in a swing out rotor at room temperature. After centrifugation the top band of cells were removed and washed 3 times with PBS w/o calcium or magnesium. The cells were centrifuged at 400x g for 10 minutes at room temperature. The cells were resuspended in Macrophage Serum Free Medium (Gibco BRL) at concentration of 2 million cells / ml.

LPS stimulation of Human PBMNC's :

PBM cells (0.1 ml ; 2 million/ml) were co-incubated with 0.1 ml of compound (10 - 0.41µM, final concentration) for 1 hour in flat bottom 96 well microtiter plate. Compounds were dissolved in DMSO initially and diluted in TCM for a final

concentration of 0.1% DMSO. LPS (Cal biochem, 20ng/ml, final concentration) was then added at volume of 0.010 ml. Cultures were incubated overnight at 37°C). Supernatant were then removed and tested by ELISA for TNF-α release. Viability was analyzed using MTT. After 0.1 ml supernatant was collected, 0.1 ml of 0.25mg/ml of MTT was added to remaining 0.1 ml of cells. The cells were incubated at 37°C for 2-4 hours, then the O.D was measured at 490-650 nm.

The TNF-α levels released in the culture medium was quantitated by ELISA. Inhibitory potency was expressed as IC_{50}.

The compounds 1 to 18 disclosed above showed p38 inhibitory activity in low μM range.

Dated this 31ST day of **January, 2005.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

ABSTRACT

ANTI-INFLAMMATORY AGENTS

The present invention relates to novel azabicyclo derivatives as anti-inflammatory agents which are useful for inhibition and prevention of inflammation and associated pathologies including inflammatory and autoimmune diseases such as sepsis, rheumatoid arthritis, inflammatory bowel disease, type-1 diabetes, asthma, chronic obstructive pulmonary disorder, organ transplant rejection and psoriasis.